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**Inhibition of proteolysis of Delta-like-1 does not promote or reduce T-cell developmental potential.**

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**Public Summary:**

**Scientific Abstract:**

Notch signaling is critical for T-cell generation in the thymus. Notch signaling is linear in nature and is highly regulated through differential gene expression and post-translational modification. Upon ligand binding, the Notch receptor is sequentially cleaved, first via extracellular ADAM protease-mediated cleavage, followed by an intracellular presenilin-dependent cleavage to release the Notch intracellular domain and activate transcription. Delta-like-1 (Dll1) is a Notch ligand that positively regulates T-cell development. Dll1 is proteolytically processed in a similar manner to the Notch receptor, and it has been speculated to participate in bidirectional signaling. We hypothesized that inhibition of Dll1 processing in Notch signal sending cells would lead to changes in their ability to support thymopoiesis. We used the OP9 in vitro co-culture system, and transduced OP9s with full length, cleavable Dll1 or a non-cleavable mutant (NC-Dll1) lacking the ADAM protease cleavage site. OP9-NC-Dll1 cells were able to support T-cell development with similar efficacy to OP9-Dll1 cells. Interestingly, expression of the Notch target gene Hes5 was more highly induced in T-cell progenitors by NC-Dll1, whereas expression of Hes1, Deltex1, and pre-Talpha were similar to controls. Furthermore, a reduced ability of hematopoietic progenitors to assume the granulocyte cell fate in OP9-NC-Dll1 cultures was noted. Taken together, these findings show that proteolytic cleavage of Dll1 in Notch signal sending cells is dispensable for murine T-cell development, differentially affects expression of Notch target genes, and might be a mechanism that regulates myelopoiesis.

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